



# Insights into the epidemiological link between biting flies and pemphigus foliaceus in southeastern Brazil



Sebastian Vernal<sup>a</sup>, Mateus Pepinelli<sup>b,c</sup>, Claudio Casanova<sup>d</sup>, Thais M. Goulart<sup>e</sup>, Olivia Kim<sup>a</sup>,  
Natalia A. De Paula<sup>a</sup>, Mara C. Pinto<sup>f</sup>, Anderson Sá-Nunes<sup>g</sup>, Ana Maria Roselino<sup>a,\*</sup>

<sup>a</sup> Division of Dermatology, Department of Clinical Medicine, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

<sup>b</sup> Department of Natural History, Royal Ontario Museum, Toronto, Ontario, Canada

<sup>c</sup> Department of Ecology and Evolutionary Biology, University of Toronto, Toronto, Ontario, Canada

<sup>d</sup> Superintendence for Endemic Disease Control, Health Secretariat of São Paulo State, Mogi-Guaçu, São Paulo, Brazil

<sup>e</sup> Institute of Biology, Department of Animal Biology, State University of Campinas, Campinas, São Paulo, Brazil

<sup>f</sup> Department of Parasitology, São Paulo State University Julio de Mesquita Filho, Araraquara, São Paulo, Brazil

<sup>g</sup> Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil

## ARTICLE INFO

### Keywords:

Pemphigus foliaceus  
Black flies  
Sandflies  
Simuliidae  
Phlebotomine

## ABSTRACT

**Background:** Black fly and sandfly bites are related to the endemicity of pemphigus foliaceus (PF); however, an immune reaction against the salivary proteins from these flies still requires confirmation in the case of PF patients living in southeastern Brazil.

**Purpose:** To georeference the distribution of Simuliidae (Diptera: Simuliidae) and Phlebotominae (Diptera: Psychodidae) and of PF cases in the northeastern region of São Paulo State, and to assess the humoral immune response against salivary gland extracts (SGEs) from biting flies in PF patients, relatives, and neighbours.

**Methods:** PF patients' medical information recorded between 1965 and 2014 were obtained from the database of the University Hospital. Data on the distribution of fly species were collected from scientific reports and epidemiological databases. Spatial maps relating the distribution of biting flies with PF cases were plotted. Serum IgG antibodies against the SGEs from *Simulium nigrimanum*, *Nyssomyia neivai*, and *Aedes aegypti* (as control) were determined by ELISA.

**Results:** Two hundred and eighty-five PF cases were distributed in 60 municipalities with a prevalence of 57.5 per million inhabitants, revealing well-defined geographical clusters. *S. nigrimanum* and *N. neivai* specimens were registered in eight (13.3%) and 26 (43.3%) of these municipalities, respectively. PF patients, and their relatives presented higher levels of IgG against the SGEs of *S. nigrimanum* and *N. neivai* ( $P < 0.001$  for both), but not against the SGE from *A. aegypti* ( $P = 0.115$  and  $P = 0.552$ , respectively), as compared to controls. IgG against the SGEs from *S. nigrimanum* and *N. neivai* but not against the SGE from *A. aegypti* correlated with levels of anti-Desmoglein 1 in PF patients ( $r = 0.3848$ ,  $P = 0.039$ ; and  $r = 0.416$ ,  $P = 0.022$ , respectively).

**Conclusion:** An epidemiological link between biting flies and PF in southeastern Brazil is proposed, implying a possible role of the salivary proteins from these flies in PF etiopathogenesis.

## 1. Introduction

Pemphigus foliaceus (PF) is an autoimmune bullous disease caused by autoantibodies against desmoglein (DSG) 1. It is subdivided into classic sporadic worldwide Cazenave's pemphigus and endemic pemphigus (known as *Fogo Selvagem* in Brazil). Although the pathogenesis of PF remains unclear, genetic and environmental factors have been implicated in the susceptibility to this disease (Abréu-Vélez et al., 2010;

Brochado et al., 2016).

Historically, PF cases have been recorded in rural areas of Brazil and other South American countries such as Colombia, Peru, Paraguay, and Venezuela (Abréu-Vélez et al., 2010; Diaz et al., 1989). That insect bites might be associated with PF has been pointed out since 1940 (Vieira, 1940), when an epidemiological link between *Simulium nigrimanum* (Macquart, 1838) and the endemicity of PF was hypothesized in São Paulo State, southeastern Brazil (Vieira, 1940). PF remains endemic in

**Abbreviations:** ATL, American Tegumentary Leishmaniasis; DSG, Desmoglein; NRSP, northeastern region of São Paulo State; SGE, salivary gland extract; PF, Pemphigus Foliaceus; VL, Visceral Leishmaniasis

\* Corresponding author at: Ribeirão Preto Medical School, University of São Paulo. Av. Bandeirantes 3900, Monte Alegre, Ribeirão Preto, São Paulo, Brazil.

E-mail address: [amfrosel@fmrp.usp.br](mailto:amfrosel@fmrp.usp.br) (A.M. Roselino).

<http://dx.doi.org/10.1016/j.actatropica.2017.09.015>

Received 27 April 2017; Received in revised form 16 August 2017; Accepted 17 September 2017

Available online 21 September 2017

0001-706X/© 2017 Elsevier B.V. All rights reserved.

the northeastern region of São Paulo State (Abréu-Vélez et al., 2010; Diaz et al., 1989; Roselino and Almeida, 1995). *S. nigrimanum* bites have been considered a risk factor for the development of PF in an Amerindian reserve in Mato Grosso do Sul State, Brazil (Aoki et al., 2004; Hans-Filho et al., 1996; Eaton et al., 1998; Lombardi et al., 1992). Two other widespread voracious black fly species—*Simulium pertinax* (Kollar, 1882) and *Simulium incrustatum* (Lutz, 1910)—have also been linked to the endemicity of PF in this same reserve (Eaton et al., 1998).

The relation between *S. nigrimanum* and other hematophagous insects with PF has been not explored enough in southeastern Brazil. Higher levels of serum IgG against maxadilan — a highly immunogenic salivary protein described in *Lutzomyia longipalpis* (Lutz and Neiva, 1912), a vector of visceral leishmaniasis (VL) (Lerner et al., 1991)—have been determined in PF patients as compared to controls living in a southeastern Brazilian region where PF is endemic (Roselino et al., 2001). There is also evidence that LJM11, another highly immunogenic protein from *Lu. longipalpis*, cross-reacts with antibodies against DSG1 (Qian et al., 2012). Zarea et al. (Zarea et al., 2012) have also reported the recognition of the salivary protein from *Phlebotomus papatasi* (Scopoli, 1786) by patients' sera in a Tunisian region where PF is endemic.

*Nyssomyia intermedia* (Lutz & Neiva, 1912) and *Nyssomyia neivai* (Pinto, 1926) (= syn. *Lutzomyia intermedia*) are the main vectors of *L. (V.) braziliensis* in São Paulo State. Moreover, *N. neivai* has been identified in research collections done systematically in several municipalities of the northeastern region of São Paulo State (Andrade Filho et al., 2007). *Lu. longipalpis* is mainly distributed in the western region of São Paulo State, but it has not been related to VL in the northeastern region of this state (Casanova et al., 2015).

Another important group of biting insect—Culicidae—has never been associated with PF; however, 23 (76%) out of 30 PF patients have reported mosquito bites in a Brazilian Amerindian reserve (Lombardi et al., 1992). Mosquitoes are vectors of various pathogens, including the Dengue and the Zika viruses, and their populations have been also reported in areas of São Paulo State where PF is endemic (Glasser and de Castro Gomes, 2000).

Considering these previous studies, the relation between the distribution of black flies and sandflies with the endemicity of PF in southeastern Brazil requires confirmation. Furthermore, assessment of PF patients exposed to bites of these flies is mandatory to establish an epidemiological link. The present study aims (i) to compare the spatial distribution of black flies (Diptera: Simuliidae) and Phlebotominae sandflies (Diptera: Psychodidae) with PF cases georeferenced in the northeastern region of São Paulo State; and (ii) to demonstrate that serum samples from PF patients recognize salivary gland extracts (SGEs) from *S. nigrimanum* (Simuliidae), *N. neivai* (Phlebotominae), and *Aedes aegypti* (Linnaeus, 1762) (Culicidae) populations from the studied region.

## 2. Materials and methods

### 2.1. Mapping and spatial distribution

#### 2.1.1. Type of study

This is an observational study with a retrospective cohort analysis

#### 2.1.2. PF cases

Medical records of PF cases were collected from the database of the University Hospital of the Ribeirão Preto Medical School, University of São Paulo, Brazil. Records concerned patients who resided in the northeastern region of São Paulo State (hereafter referred as NRSP) at the onset of PF symptoms between 1965 and 2014. The clinical diagnosis of PF was confirmed by acantholytic bullae on the histopathological examination, positive IgG fluorescence around keratinocytes in skin samples, and presence of serum autoantibodies against DSG1 as revealed by ELISA (MBL, Nagoya, Japan).

#### 2.1.3. Study area

NRSP, southeastern Brazil, has a tropical climate and is located between 19°52' and 22°51'S and 46°16' and 49°20'W. The region comprises 125 municipalities that cover an area of 51,661 km<sup>2</sup>. This region represents about 21% of the total area of the state and was inhabited by 5,156,660 people in 2016 (IBGE, 2017).

#### 2.1.4. Data on black flies

Reports of *S. nigrimanum* collections in NRSP have been registered since the beginning of the last century (Vieira, 1940). Most data were obtained from Dr Mateus Pepinelli doctoral thesis, in which he reports collecting specimens from 151 streams and rivers across São Paulo State, of which 26 were situated in 25 NRSP municipalities. Collections were accomplished between 2002 and 2005 (Pepinelli, 2008).

#### 2.1.5. Data on sandflies

The distribution of sandflies was obtained from epidemiological data deposited at the database of the Health Secretariat of São Paulo State since 1940, obtained mainly via the VL and American tegumentary leishmaniasis (ATL) surveillance programs. Entomological collections were performed in locations with known or suspected human cases of ATL and in municipalities with suspected or confirmed cases of human and canine VL; a minimum of four dwellings were sampled (Casanova et al., 2015; Casanova et al., 2014; Secretary of Health of São Paulo State, 2011; Secretary of Health of São Paulo State, 2008).

#### 2.1.6. Spatial maps

The scale for map construction was 1:3,266,000 kilometres (0–130.7 latitude/longitude projection). Cases were plotted against the number of patients in each municipality of NRSP. Black fly and sandfly records were also plotted per municipality.

#### 2.1.7. Nomenclature

Nomenclature of insect species follows Galati and Adler & Crosskey's guidelines (Adler and Crosskey, 2015; Galati, 2003). Abbreviation of generic names for sandflies follows Marcondes' guidelines (Marcondes, 2007).

## 2.2. Assessment of exposure to bites

### 2.2.1. Type of study

This is a transversal study

### 2.2.2. Samples of insects

Given their pest status and wide distribution, *S. nigrimanum* and *N. neivai* were included as the most representative simuliid and phlebotomine, respectively, of the target region. *A. aegypti*—another biting fly that is widely distributed in NRSP (Glasser and de Castro Gomes, 2000) but which has not been related to PF—was included as a control.

**2.2.2.1. *Simulium nigrimanum*.** Adult females were collected in Ribeirão Corrente river, in the municipality of Jardínópolis, NRSP (20°30'30.04"S, 47°33'04.34"W) during oviposition, while flying, or while biting humans. Aquatic life stages were collected for additional identification, following Hamada & Pepinelli methods (Hamada and Pepinelli, 2004).

**2.2.2.2. *Nyssomyia neivai*.** Adult female samples were obtained from a laboratorial colony supervised by Dr Mara Pinto, State University of São Paulo, Araraquara, Brazil.

**2.2.2.3. *Aedes aegypti*.** Adult female samples were obtained from a laboratorial colony supervised by Dr Anderson Sá-Nunes, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil.

Download English Version:

<https://daneshyari.com/en/article/5671057>

Download Persian Version:

<https://daneshyari.com/article/5671057>

[Daneshyari.com](https://daneshyari.com)